IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

von BORSTEL et al	Atty. Ref.: **1331-138**
Serial No. **08/460,186**	Group: **1623**
Filed: **June 2, 1995**	Examiner: **Kunz, G.**

For: **TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES**

* *

May 14, 2001

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

SUPPLEMENTAL APPEAL BRIEF

Sir:

This is supplemental to the Appeal Brief filed October 13, 2000. In that Brief, is was stated, in the Grouping of Claims section, that Claims 1-25 which are the subject of the present appeal, "stand or fall depending on the outcome of the Board's Decision." Upon further consideration, Appellants would like to modify that statement. In particular, it is believed that claims 18-19 are nonobvious and do not stand or fall with the other claims on appeal.

As stated in the Appeal Brief, it is presumed reliance on Falcone has been withdrawn." (Appeal Brief, p. 6), since Falcone is not mentioned in the June 16, 1998 Office Action in connection with the rejection under 35 U.S.C. §103 of

claims 1-15, 18-19 and 22-25. Falcone has been cited in earlier Office Actions. and without reliance on Falcone it is not seen how the rejection of claims 18-19 can be maintained. Until it is confirmed that reliance on Falcone has been withdrawn, Appellants wish to present arguments against a rejection of claims 18-19 based on Falcone et al. in combination with the other references.

Claims 18-19 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal an acylated derivative of uridine, deoxyuridine or cytidine; and an inhibitor of uridine phosphorylase. Falcone, et al., Blood (1990) 76(11): 2216-2221 has been cited as a secondary reference teaching the use of an inhibitor of uridine nucleoside phosphorylase, benzylacylouridine (BAU) to increase the serum and tissue levels of free uridine, and thereby reducing the toxicity of AZT. Based on Falcone, et al. in combination with the Martin or Sommadossi and von Borstel publications, it allegedly would have been obvious to administer acylated uridine or cytidine in combination with a uridine phosphorylase inhibitor to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine.

The teaching of Falcone would not have motivated one to combine an inhibitor of uridine phosphorylase with a source of uridine, since Falcone et al. teaches that the increased *in vivo* levels of uridine resulting from such combination did not result in reductions in AZT toxicity as compared to the

uridine phosphorylase inhibitor BAU alone. This can be seen from Falcone, et al., which states:

> "Indeed, our present observation that BAU doses above 300 mg/kg/d, or combinations of BAU with low doses of exogenous Urd, do not result in improved therapeutic efficacy as compared with BAU alone (300 mglkg/d) supports previous in vitro observations that the maximum ability of exogenous Urd to reverse AZT cytotoxicity is achieved at the relatively low Urd concentration of 50 μmol/L." (Falcone, et al., paragraph bridging pp. 2219-2220)

As seen from the above-quoted passage from Falcone, the person of ordinary skill in the art would not have expected that the combination of a uridine phosphorylase inhibitor (such as BAU) and a source of uridine would result in improved therapeutic efficacy, compared to the uridine phosphorylase inhibitor alone. In the absence of such an expectation, there would have been no motivation to adminster an acyl derivative of uridine in combination with an inhibitor of uridine phosphorylase.

Reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

von BORSTEL et al — Atty. Ref.: 1331-138

Serial No. 08/460,186 — Group: 1623

Filed: June 2, 1996 — Examiner: Kunz, G.

For: TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES

* * * * * * * * * * *

May 14, 2001

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

Attached is a completed Form PTO-1449 listing U.S. patent 5,968,914 and a reference to Kralovansky, et al., Cancer Chemother Pharmacol (1993) 32: 243-248. A copy of each of these references is attached.

For completeness, the Examiner is advised that Claims 1-36 in Application No. 08/472,210 (now U.S. Patent 5,968,914), claims 27-47 in Application No. 08/464,944, and claims 48-74 in Application No. 08/473,332 were provisionally rejected on grounds of obviousness-type double patenting over claims 1-25 of the subject application. Copies of those claims are attached.

The Examiner is requested to initial the attached PTO-1449, and to return a copy of the initialed document to the undersigned as an indication that the listed references have been considered and made of record.

Respectfully submitted,

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May 14, 2001

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

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The Examiner is requested to initial the attached PTO-1449, and to return a copy of the initialed document to the undersigned as an indication that the listed references have been considered and made of record.

Respectfully submitted,

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Sheet 1 of 1

INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

ATTY. DOCKET NO.: 1331-138

SERIAL NO.: 08/460,186

APPLICANT: von BORSTEL et al

FILING DATE: June 2, 1996

GROUP:

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		5,968,914	10/1999	Von Borstel et al.			

FOREIGN PATENT DOCUMENTS

		DOCUMENT	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO

OTHER DOCUMENTS (including Author, Title, Date, Pertinent pages, etc.)

		Kralovansky, et al., Cancer Chemother Pharmacol (1993) 32: 243-248.

*Examiner | Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to application.

Form PTO-FB-A820 (Also PTO-1449)

525131

CLAIMS

What is claimed is:

1. A method for treating cancer comprising:
(a) administering a pyrimidine nucleoside analog in a dose at least 1.5 fold greater than the normal maximum tolerated dose, and
(b) administering a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

2. A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine or 2'- deoxyfluorouridine, fluorocytosine, trifluoro-methyl-2'-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

3. A method as in claim 1 wherein said pyrimidine nucleoside analog is a 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, or deoxyuridine.

4. A method as in claim 3 wherein said 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil, 5-

fluorouracil prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine, prodrug derivatives of 2'- deoxyfluorouridine, 5-fluorocytosine, 5-fluorocytidine, or prodrug derivatives of 5-fluorocytidine.

5. A method as in claim 3 wherein said 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog is 5-fluorouracil.

6. A method as in claim 5 wherein said administering step (a) comprises administering a bolus of 900 to 2400 mg/m² of 5-fluorouracil, and said administering step (b) comprises administering 2 to 24 hours after step (a) 1 to 10 grams of an acyl derivative of a nonmethylated pyrimidine nucleoside, wherein steps (a) and (b) are repeated 3-6 times.

7. A method as in claim 6 wherein the time interval between each repetition of step (a) is 4 to 14 days.

8. A method as in claim 5 wherein said administering step (a) comprises administering a bolus of 600 to 1000 mg/m² of 5-fluorouracil daily for 4 to 5 consecutive days, and said administering step (b) comprises administering 2 to 12 hours after each step (a) 1 to 10 grams of an acyl derivative of a nonmethylated pyrimidine nucleoside.

9. A method as in claim 1 wherein said pyrimidine nucleoside analog is N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, trifluoromethyl-2'-deoxyuridine, or 3-deazauridine and said acyl

derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine or cytidine.

10. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine or deoxyuridine.

11. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

12. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

13. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetylcytidine.

14. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

15. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antineoplastic analog of cytidine and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of deoxycytidine.

16. A method as in claim 15 wherein said antineoplastic analog of cytidine is arabinosyl cytosine or prodrugs thereof, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, or 6-azacytidine.

17. A method as in claim 1 wherein said pyrimidine nucleoside analog is an analog of uridine, said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step (b) also includes administering an inhibitor of uridine phosphorylase.

18. A method as in claim 17 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclouridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

19. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of cytidine deaminase.

20. A method as in claim 19 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

21. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of nucleoside transport.

22. A method as in claim 21 wherein said inhibitor of nucleoside transport is selected from the group consisting of dilazep, dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

23. A method as in claim 1 wherein said administering step (b) also includes administering an agent which enhances hematopoiesis.

24. A method as in claim 1 wherein said administering step (b) also includes administering a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

25. A method as in claim 1 wherein said administering step (a) also includes administering AZT.

26. A method as in claim 1 wherein said fluorinated pyrimidine is administered in conjunction with a biochemical modulator of 5-fluorouracil efficacy.

27. A method as in claim 26 wherein said modulator is an inhibitor of purine biosynthesis, an antifolate, an inhibitor of pyrimidine biosynthesis, or an inhibitor of 5-fluorouracil degradation.

28. A method as in claim 27 wherein said inhibitor of purine biosynthesis is methylmercaptopurine riboside.

29. A method as in claim 27 wherein said antifolate is methotrexate or trimetrexate.

30. A method as in claim 27 wherein said inhibitor of pyrimidine biosynthesis is PALA, brequinar, acivicin, or 6-azauridine.

31. A method as in claim 27 wherein said inhibitor of 5-fluorouracil degradation is an inhibitor of the enzyme dihydropyrimidine dehydrogenase.

32. A method as in claim 31 wherein said inhibitor of dihydropyrimidine dehydrogenase is 5-ethynyluracil, bromovinyluracil, CDHP, uracil, thymine, thymidine or benzyloxybenzyluracil.

33. A method for treating cancer comprising:
(a) administering an inhibitor of the enzyme dihydropyrimidine dehydrogenase;
(b) administering a 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog;
(c) administering a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

34. A method as in claim 33 wherein said 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil, 5-fluorouracil prodrugs including tegafur and 5'-

deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine, prodrug derivatives of 2'-deoxyfluorouridine, 5-fluorocytosine, 5-fluorocytidine, or prodrug derivatives of 5-fluorocytidine.

35. A method as in claim 33 wherein said inhibitor of dihydropyrimidine dehydrogenase is 5-ethynyluracil, bromovinyluracil, cyanodidhydropyridine, uracil, thymine, thymidine or benzyloxybenzyluracil.

36. A method as in claim 33 wherein said administering step (a) takes place before or at the same time as said administering step (b).

CLAIMS

What is claimed is:

1. A method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

2. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine, or deoxyuridine.

3. A method as in claim 1 wherein said toxicity is damage to hematopoietic tissue.

4. A method as in claim 1 wherein said toxicity is damage to mucosal tissues.

5. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antineoplastic agent.

6. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antiviral agent.

7. A method as in claim 1 wherein said pyrimidine nucleoside analog is an antimalarial agent.

8. A method as in claim 1 wherein said pyrimidine nucleoside analog is a cytotoxic analog of uridine.

9. A method as in claim 1 wherein said pyrimidine nucleoside analog is a cytotoxic analog of cytidine.

10. A method as in claim 1 wherein said pyrimidine nucleoside analog is an inhibitor of pyrimidine nucleotide biosynthesis.

11. A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine or 2'- deoxyfluorouridine, fluorocytosine, trifluoro-methyl-2'-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-azá-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

12. A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of AZT, dideoxycytidine, 5-ethyl-2'-deoxyuridine, 5-iodo-2'-deoxyuridine, 5-bromo-2'-deoxyuridine, 5-methylamino-2'-deoxyuridine, arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine.

13. A method as in claim 1 wherein said pyrimidine nucleoside analog is 5-fluoroorotate.

14. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

15. A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

16. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is triacetylcytidine.

17. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

18. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step also includes administering an inhibitor of uridine phosphorylase.

19. A method as in claim 18 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclo-uridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, and hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate,

5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

20. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or deoxycytidine, and said administering step also includes administering an inhibitor of cytidine deaminase.

21. A method as in claim 20 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

22. A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step also includes administering an inhibitor of nucleoside transport.

23. A method as in claim 22 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

24. A method as in claim 1 wherein said administering step also includes administering an agent which enhances hematopoiesis.

25. A method as in claim 1 wherein said administering step also includes administering a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

26. A method for preventing an opportunistic infection after chemotherapy comprising administering to an animal a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

27. A method for treating cancer comprising: (a) administering a pyrimidine nucleoside analog, and (b) administering a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

28. A method as in claim 27 wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine or 2'- deoxyfluorouridine, fluorocytosine, trifluoro-methyl-2'-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

29. A method as in claim 27 wherein said pyrimidine nucleoside analog is a 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, or deoxyuridine.

30. A method as in claim 29 wherein said 5-fluoropyrimidine or 5-fluoropyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil, 5-

fluorouracil prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'-deoxyfluorouridine, prodrug derivatives of fluorouridine, prodrug derivatives of 2'- deoxyfluorouridine, 5-fluorocytosine, 5-fluorocytidine, or prodrug derivatives of 5-fluorocytidine.

31. A method as in claim 27 wherein said pyrimidine nucleoside analog is N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, trifluoromethyl-2'-deoxyuridine, or 3-deazauridine and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine or cytidine.

32. A method as in claim 27 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine or deoxyuridine.

33. A method as in claim 27 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

34. A method as in claim 27 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

35. A method as in claim 27 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetylcytidine.

36. A method as in claim 27 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

37. A method as in claim 27 wherein said pyrimidine nucleoside analog is an antineoplastic analog of cytidine and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of deoxycytidine.

38. A method as in claim 37 wherein said antineoplastic analog of cytidine is arabinosyl cytosine or prodrugs thereof, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, or 6-azacytidine.

39. A method as in claim 27 wherein said pyrimidine nucleoside analog is an analog of uridine, said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step (b) also includes administering an inhibitor of uridine phosphorylase.

40. A method as in claim 39 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclo-uridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate,

5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

41. A method as in claim 27 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of cytidine deaminase.

42. A method as in claim 41 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

43. A method as in claim 27 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of nucleoside transport.

44. A method as in claim 43 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

45. A method as in claim 27 wherein said administering step (b) also includes administering an agent which enhances hematopoiesis.

46. A method as in claim 27 wherein said administering step (b) also includes administering a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

47. A method as in claim 27 wherein said administering step (a) also includes administering AZT.

48. A method for treating a viral infection comprising:
(a) administering a pyrimidine nucleoside analog, and
(b) administering a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

49. A method as in claim 48 wherein said viral infection is AIDS.

50. A method as in claim 48 wherein said viral infection is herpes.

51. A method as in claim 48 wherein said viral infection is hepatitis.

52. A method as in claim 48 wherein said pyrimidine nucleoside analog is selected from the group consisting of AZT, dideoxycytidine, 2',3'-dideoxycytidin-2'-ene, 3'-deoxythymidin-2'-ene, 3'-azido-2',3'-dideoxyuridine, 5-ethyl-2'-deoxyuridine, 5-iodo-2'-deoxyuridine, 5-bromo-2'-deoxyuridine, 2',3'-dideoxy-3'-fluorothymidine, 5-methylamino-2'-deoxyuridine, arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine.

53. A method as in claim 48 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine or deoxyuridine.

54. A method as in claim 48 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

55. A method as in claim 48 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

56. A method as in claim 48 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is triacetylcytidine.

57. A method as in claim 48 wherein said an acyl derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

58. A method as in claim 48 wherein said pyrimidine nucleoside analog is AZT and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, or deoxycytidine.

59. A method as in claim 48 wherein said pyrimidine nucleoside analog is dideoxycytidine said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of deoxycytidine.

60. A method as in claim 48 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step (b) also includes administering an inhibitor of uridine phosphorylase.

61. A method as in claim 60 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclouridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

62. A method as in claim 48 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of cytidine deaminase.

63. A method as in claim 62 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

64. A method as in claim 48 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step (b) also includes administering an inhibitor of nucleoside transport.

65. A method as in claim 64 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

66. A method as in claim 48 wherein said administering step (b) also includes administering an agent which enhances hematopoiesis.

67. A method as in claim 48 wherein said administering step (b) also includes administering a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

68. A method for treating a viral infection comprising:
(a) administering a pyrimidine nucleoside analog, and
(b) administering a pharmaceutically effective amount of an inhibitor of deoxycytidine deaminase.

69. A method as in claim 68 wherein said pyrimidine analog is selected from the group consisting of AZT or dideoxycytidine.

70. A method as in claim 68 wherein said inhibitor of deoxycytidine deaminase is tetrahydrouridine or tetrahydro-2'-deoxyuridine.

71. A method for treating a malarial infection comprising:
(a) administering a pyrimidine nucleoside analog, and

(b) administering a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

72. A method as in claim 71 wherein said pyrimidine nucleoside analog is 5-fluoroorotate and said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine or cytidine.

73. A method as in claim 71 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine or cytidine, and said administering step (b) also includes administering an inhibitor of uridine phosphorylase.

74. A method as in claim 73 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclouridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

75. A composition comprising:
an acyl derivative of a non-methylated pyrimidine nucleoside ;and
an antineoplastic agent.

76. A composition as in claim 75 wherein said antineoplastic agent is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including tegafur and 5'-deoxyfluorouridine, fluorouridine, 2'- deoxyfluorouridine, prodrug derivatives of fluorouridine or 2'-deoxyfluorouridine, fluorocytosine, trifluoro-methyl-2'-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

77. A composition as in claim 75, wherein said acyl derivative of a non-methylated pyrimidine nucleoside is a an acyl derivative of cytidine, and said antineoplastic agent is an analog of cytidine.

78. A composition as in claim 77 wherein said antineoplastic analog of cytidine is arabinosyl cytosine or prodrugs thereof, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, or 6-azacytidine.

79. A composition as in claim 75, wherein said acyl derivative of a non-methylated pyrimidine nucleoside is deoxycytidine, and said antineoplastic agent is an analog of cytidine.

80. A composition as in claim 79 wherein said analog of cytidine is arabinosyl cytosine or prodrugs thereof, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, or 6-azacytidine.

81. A composition as in claim 75, wherein said acyl derivative of a non-methylated pyrimidine nucleoside is a an acyl derivative of uridine, and said antineoplastic agent is a fluorinated pyrimidine.

82. A composition as in claim 81 wherein said fluorinated pyrimidine is tegafur, 5'-deoxyfluorouridine, 5-fluorouracil, 5-fluorouridine, N^4-trimethoxybenzoyl-5'-deoxy-5-fluorocytidine, or 2'deoxy-5-fluorouridine, or acyl derivatives thereof.

83. A composition as in claim 81, wherein the molar ratio of said acyl derivative of uridine to said fluorinated pyrimidine is 1:1 to 12:1.

84. A composition as in claim 81, wherein the molar ratio of said acyl derivative of uridine to said fluorinated pyrimidine is 2:1 to 8:1.

85. A composition as in claim 81, wherein the molar ratio of said acyl derivative of uridine to said fluorinated pyrimidine is 4:1.

86. A composition as in claim 81, wherein said acyl derivative of uridine is triacetyluridine, and said antineoplastic agent is a fluorinated pyrimidine.

87. A composition as in claim 81, wherein said acyl derivative of uridine is triacetyluridine, and said antineoplastic agent is tegafur.

88. A composition comprising:
an acyl derivative of a non-methylated pyrimidine nucleoside

;and

an antiviral agent.

89. A composition as in claim 88, wherein said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, or deoxycytidine, and said antiviral agent is AZT.

90. A composition as in claim 88 wherein said antiviral agent is selected from the group consisting of AZT, dideoxycytidine, 2',3'-dideoxycytidin-2'-ene, 3'-deoxythymidin-2'-ene, 3'-azido-2',3'-dideoxyuridine, 5-ethyl-2'-deoxyuridine, 5-iodo-2'-deoxyuridine, 5-bromo-2'-deoxyuridine, 2',3'-dideoxy-3'-fluorothymidine, 5-methylamino-2'-deoxyuridine, arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine.

91. A composition comprising:

an acyl derivative of a non-methylated pyrimidine nucleoside ;and

an antimalarial agent.

92. A composition as in claim 91, wherein said acyl derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine or cytidine, and said antimalarial agent is 5-fluoroorotate.

93. A composition as in claim 91 wherein said antimalarial agent is selected from the group consisting of 5-fluoroorotate, PALA, or 6-azauridine.

94. A composition comprising:

an acyl derivative of a non-methylated pyrimidine nucleoside ;and

an agent which enhances hematopoiesis.

95. A composition as in claim 94, wherein said agent which enhances hematopoiesis is selected from the group consisting of a nonionic surfactant, an interleukin, a colony-stimulating factor, erythropoietin, glucan, and polyinosine-polycytidine.

96. A composition as in claim 94, wherein said agent which enhances hematopoiesis is an oxypurine nucleoside, a congener of an oxypurine nucleoside, or an acyl derivative of an oxypurine nucleoside or an oxypurine nucleoside congener.

97. A composition comprising:

an acyl derivative of a non-methylated pyrimidine nucleoside ;and

a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

98. A composition as in claim 97, wherein said compound capable of enhancing uptake and phosphorylation of nucleosides into cells is selected from the group consisting of insulin and an insulinogenic carbohydrate.

99. A composition comprising

an acyl derivative of a non-methylated pyrimidine nucleoside ;and

an agent capable of promoting healing of mucosal tissue.

100. A composition as in claim 99 wherein said agent capable of promoting healing of mucosal tissue is selected from the group consisting of sucralfate, a mixture of two or more deoxyribonucleosides, allopurinol, an antibiotic or a local anesthetic.

101. A composition comprising
an acyl derivative of uridine
;and
a compound capable of inhibiting uridine phosphorylase.

102. A composition as in claim 101 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclo-uridine, aminomethyl-benzylacyclouridine, aminomethyl-benzyloxybenzylacyclouridine, hydroxymethyl-benzylacyclouridine, hydroxymethyl-benzyloxybenzyl-acyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

103. A composition comprising:
an acyl derivative of cytidine or deoxycytidine
;and
a compound capable of inhibiting deoxycytidine deaminase.

104. A composition as in claim 103 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

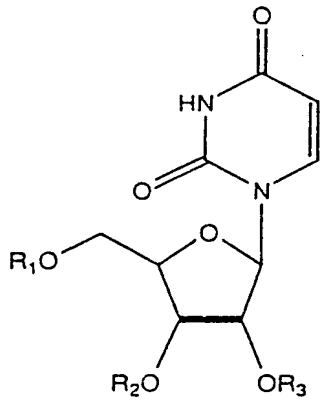
105. A composition comprising:

an acyl derivative of uridine, cytidine, or deoxycytidine ;and

a compound capable of inhibiting nucleoside transport.

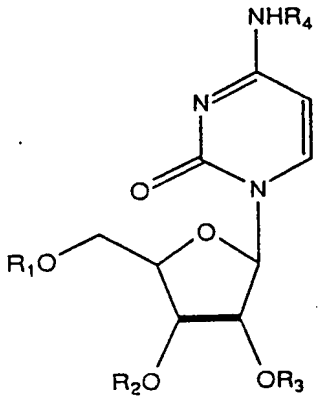
106. A method as in claim 105 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or nitrobenzylthioinosine.

107. An acyl derivative of uridine having the formula:



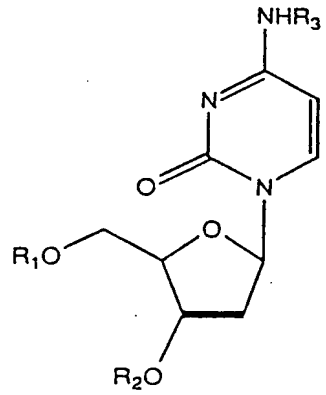
wherein at least one of R_1, R_2, or R_3 is a hydrocarbyloxycarbonyl moiety containing 2-26 carbon atoms and the remaining R substituents are independently a hydrocarbyloxycarbonyl or hydrocarbylcarbonyl moiety or H or phosphate.

108. An acyl derivative of cytidine having the formula:



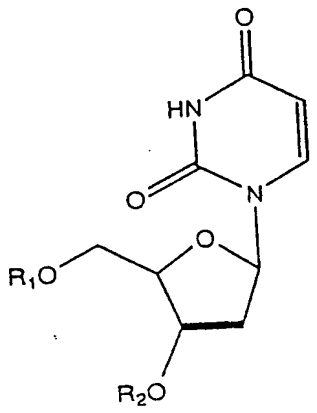
wherein at least one of R_1, R_2, R_3 or R_4 is a hydrocarbyloxycarbonyl moiety containing 2-26 carbon atoms and the remaining R substituents are independently a hydrocarbyloxycarbonyl or hydrocarbylcarbonyl moiety or H or phosphate.

109. An acyl derivative of deoxycytidine having the formula:



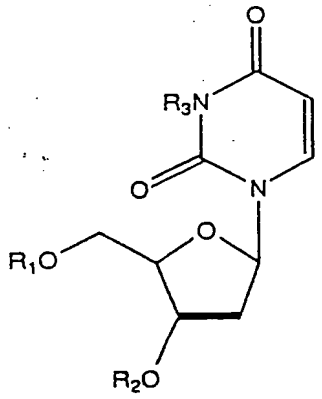
wherein at least one of R_1, R_2, or R_3 is a hydrocarbyloxycarbonyl moiety containing 2-26 carbon atoms and the remaining R substituents are independently a hydrocarbyloxycarbonyl or hydrocarbylcarbonyl moiety or H or phosphate.

110. An acyl derivative of deoxyuridine having the formula:



wherein at least one of R_1 or R_2 is a hydrocarbyloxycarbonyl moiety containing 2-26 carbon atoms and the remaining R substituents are independently a hydrocarbyloxycarbonyl or hydrocarbylcarbonyl moiety or H or phosphate.

111. An acyl derivative of deoxyuridine, having the formula



wherein R_1, R_2, and R_3 are the same, or different, and each is hydrogen or an acyl radical derived from

a. an unbranched fatty acid with 3 to 22 carbon atoms,

b. an amino acid selected from the group consisting of glycine, the L forms of alanine, valine, leucine, isoleucine, tyrosine, proline, hydroxyproline, serine, threonine, cystine, cysteine, aspartic acid, glutamic acid, arginine, lysine, histidine, carnitine and ornithine,

c. nicotinic acid

d. a dicarboxylic acid having 3-22 carbon atoms,

provided that not all of R_1, R_2, and R_3 are H, and where R_3 is not H, then R_1 and/or R_2 may also be acetyl, or a pharmaceutically acceptable salt thereof.

112. A pharmaceutical composition comprising a compound of claims 107, 108, 109, 110, or 111 and a pharmaceutically acceptable carrier.